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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,689	11/24/2003	Mario Stevenson	UMY-034	3913
959 7590 04/30/2008 LAHIVE & COCKFIELD, LLP ONE POST OFFICE SQUARE BOSTON, MA 02109-2127				
EXAMINER SCHNIZER, RICHARD A				
ART UNIT		PAPER NUMBER		
1635				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/722,689

Applicant(s)

STEVENSON ET AL.

Examiner

Richard Schnizer, Ph. D.

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 July 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21, 23-44 and 75-94 is/are pending in the application.
- 4a) Of the above claim(s) 23-44 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-21 and 75-94 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 24 November 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 2/19/08
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

An amendment was received and entered on 2/19/08.

Claims 22 and 45-74 were canceled.

Claims 1-21, 23-44, and 75-94 are pending. Claims 23-44 stand withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/17/06.

Claims 1-21 and 75-94 are under consideration in this Office Action.

Rejections not reiterated from the previous action are withdrawn.

The Declaration of Mario Stevenson and Jean-Marc Jacque was fully considered and was sufficient to overcome the rejection of claims 1-3, 8-11, 14-22, 77-81, 84, and 86-94 over McSwiggen.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-11, 14-21, 75-84, and 86-94 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Draper et al (US 5693535) in view of Tuschl et al (US 7056704).

Draper taught ribozymes targeting various conserved sites in HIV RNA such as LTR, nef, vif, tat and rev. See column 4, lines 1-3 and 10-15; and column 9, lines 57-66. Note that some of the vif-targeted ribozymes also target pol. See column 10, lines 43-45.

Draper did not teach siRNA.

Tuschl taught siRNAs of 21-24 nucleotides (preferably 21 nucleotides) that are structurally and functionally equivalent to dicer cleavage products of longer dsRNAs. See column 28, lines 15-17. The siRNAs may contain modified nucleotides (column 3, lines 36-44), and mismatches relative to the target sequence are allowed at the termini of the siRNAs (column 28, lines 25-32), for example it is routine to include terminal TT dinucleotides regardless of the target sequence.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute siRNAs of Tuschl for the ribozymes of Draper when targeting HIV RNA for degradation. One would have been motivated to do so because siRNAs are more potent than ribozymes. Tuschl et al stated that "siRNAs are extraordinarily powerful reagents for mediating gene silencing" and that "siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments." See column 23, lines 15-20. One would have had a reasonable expectation of success because the target sites of Draper were selected on the basis of their availability for hybridization. See column 10, lines 13-23, and 52-63.

The "expressed from a vector" limitation of claim 84, 86 and 87 does not affect the structure of the siRNA, and so receives it no patentable weight. Similarly, claims 88-93 are included in this rejection because although they recite structural requirements of a vector (e.g. the vector must encode a plurality of siRNAs), these vector structure requirements are given no patentable weight because the claims are drawn to "a small interfering RNA (siRNA)", and not to a vector. The particulars of the vector are not considered to have any effect on the structure of the claimed siRNA, and so are given no patentable weight.

Claims 12, 13, and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Draper et al (US 5693535) and Tuschl et al (US 7056704) as applied to claims 1-11, 14-22, 75-84, and 86-94 above, and further in view of Svoboda et al (Biochem. Biophys. Res. Comm. 287: 1099-1104, 2001).

The teachings of Draper and Tuschl are summarized above and can be combined to render obvious siRNAs directed to portions of an HIV genome. The references did not explicitly disclose shRNAs.

Svoboda taught that shRNAs, expressed from plasmids, were just as effective as dsRNAs comprising separate strands. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute shRNA for siRNA in the invention of Draper as modified by Tuschl. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function,

such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). Finally, the substitution of shRNA for siRNA would have yielded predictable results to one of ordinary skill in the art at the time of the invention, in view of the teachings of Svoboda. Thus the invention as a whole was prima facie obvious.

Note, the statement of the rejection above corrects a typographical error in the previous action that indicated that the rejected claims were 13, 14, and 85, instead of 12, 13, and 85. This was clearly a typographical error in view of the fact that claims 12, 13, and 85 are drawn to shRNAs, as are the teachings of Svoboda.

Response to Arguments

Applicant's arguments filed 2/19/08 have been fully considered, but are not persuasive.

Applicant argues at page 13 of the response that one of ordinary skill would not have been motivated to turn to the ribozyme art in order to arrive at the instant invention because siRNAs which act by guiding a catalytic RNA-induced silencing complex, and ribozymes which are catalytic themselves, are structurally and functionally distinct from each other. This is unpersuasive. One would clearly have been motivated to turn from

the ribozyme art to the siRNA art because one of ordinary skill appreciated that both reagents were meant to be used to degrade target RNAs, and because Tuschl stated that "siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments." See column 23, lines 15-20. Therefore, one of ordinary skill, aware of the teachings of both Draper and Tuschl would have been motivated to substitute siRNAs for ribozymes.

Applicant argues further that one of ordinary skill would have had no reasonable expectation of success in applying siRNA technology to HIV. Applicant asserts that it was thought that the genomic RNA of RNA viruses would not be amenable to siRNA degradation. For support, Applicant relies on Bitko (2001) at page 8, first full paragraph of column 2, stating that Bitko found that genomic RNA of respiratory syncytial virus was resistant to degradation by siRNAs, and that Bitko suggested that the target genomic RNA was inaccessible due to encapsidation within the nucleocapsid.

This is unpersuasive for several reasons. First, there is no evidence of record that HIV genomic RNA in nucleocapsid form is as inaccessible to siRNA as RSV genomic RNA. Second, nucleocapsid proteins must be removed from the genomic RNA during replication in order to allow reverse transcriptase access to the template. At this time one would reasonably expect the genome to be vulnerable to siRNA. This is supported by the evidence of record. Park et al (Nucleic Acids Research. Supplement (2001), No. 1, pp. 219-20)) showed that dsRNAs inhibited HIV replication in COS cells. Third, there is no reason of record to believe that siRNAs would not inhibit

HIV gene expression from integrated proviral genomes which are expressed in the absence of the nucleocapsid. Accordingly, and particularly in view of the findings of Park (2001, of record) one of ordinary skill would have had ample reason to expect success. For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

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If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Richard Schnizer, Ph. D./
Primary Examiner, Art Unit 1635